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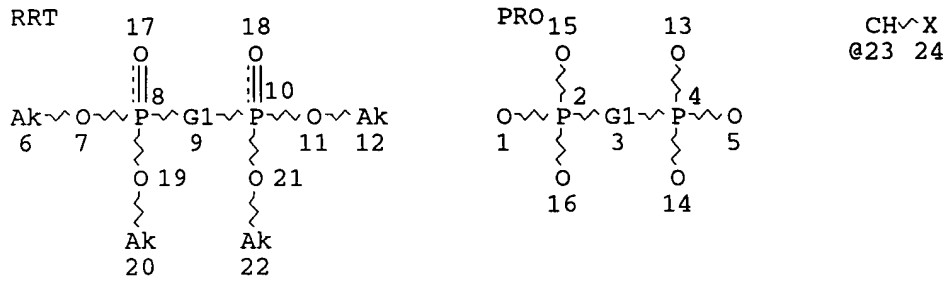

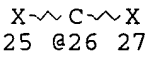


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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  27

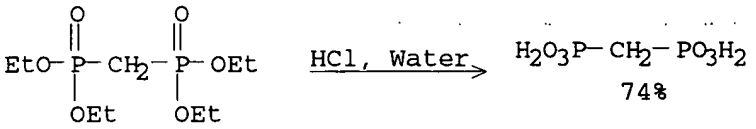
STEREO ATTRIBUTES: NONE
L3            12 SEA FILE=CASREACT SSS FUL L1 (    30 REACTIONS)


=> d l3 ibib abs crd 1-12


L3   ANSWER 1 OF 12  CASREACT  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         139:332355  CASREACT
TITLE:                    Bisphosphonates derived from fatty acids are potent
                          inhibitors of Trypanosoma cruzi farnesyl pyrophosphate
                          synthase
AUTHOR(S):                Szajnman, Sergio H.; Montalvetti, Andrea; Wang,
                          Youhong; Docampo, Roberto; Rodriguez, Juan B.
CORPORATE SOURCE:         Facultad de Ciencias Exactas y Naturales, Departamento
                          de Quimica Organica, Universidad de Buenos Aires,
                          Buenos Aires, C1428EHA, Argent.
SOURCE:                   Bioorganic & Medicinal Chemistry Letters (2003),
                          13(19), 3231-3235
                          CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:                Elsevier Science B.V.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Studies on the mode of action of a series of bisphosphonates derived from
```

fatty acids, which had previously proved to be potent inhibitors against Trypanosoma cruzi proliferation in in vitro assays, have been performed. Some of these drugs proved to be potent inhibitors against the intracellular form of the parasite, exhibiting IC50 values at the low micromolar level. As bisphosphonates are FDA clin. approved for treatment of bone resorption disorders, their potential innocuousness makes them good candidates to control tropical diseases.

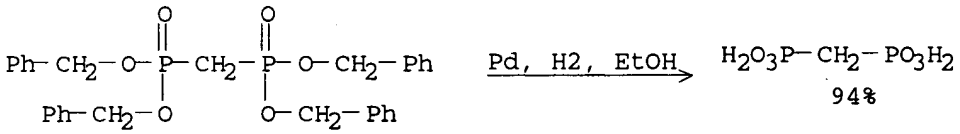
RX(1) OF 34



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 136:386188 CASREACT
TITLE: Simple synthesis of oxiranylidene-2,2-bis(phosphonic acid): tetrabenzyl geminal bisphosphonate esters as useful intermediates
AUTHOR(S): Page, Philip C. Bulman; McKenzie, Michael J.; Gallagher, James A.
CORPORATE SOURCE: Department of Chemistry, Loughborough University, Loughborough, LE11 3TU, UK
SOURCE: Synthetic Communications (2002), 32(2), 211-218
CODEN: SYNCAV; ISSN: 0039-7911
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tetrabenzyl geminal bisphosphonate esters are useful synthetic equivalent of 1,1-bis(phosphonic acid)s which may be easily functionalized at the central C atom without phosphonate ester hydrolysis. The parent bis(phosphonic acid) unit is readily regenerated by hydrogenolysis. The chemical was used to prepare the elusive epoxide oxiranylidene-2,2-bis(phosphonic acid) by a short and reliable procedure.

RX(3) OF 23



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 134:252473 CASREACT
TITLE: Process for preparing methylenebisphosphonic acid

salts
INVENTOR(S): Purdie, Mark
PATENT ASSIGNEE(S): Astrazeneca UK Limited, UK
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001021629	A1	20010329	WO 2000-GB3473	20000911
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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EP 1216253	A1	20020626	EP 2000-958856	20000911
EP 1216253	B1	20030611		
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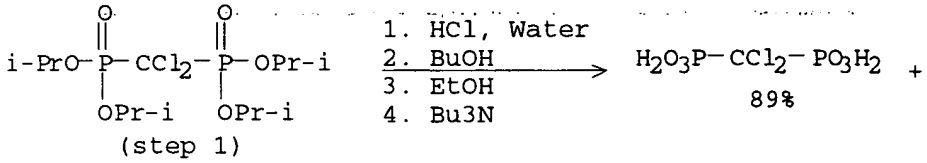
JP 2003509517	T2	20030311	JP 2001-525004	20000911
AT 242778	E	20030615	AT 2000-958856	20000911
NZ 517552	A	20030926	NZ 2000-517552	20000911
PT 1216253	T	20031031	PT 2000-958856	20000911
ES 2200921	T3	20040316	ES 2000-958856	20000911
AU 771628	B2	20040401	AU 2000-70270	20000911
ZA 2002001661	A	20030527	ZA 2002-1661	20020227
NO 2002001269	A	20020314	NO 2002-1269	20020314
US 6657076	B1	20031202	US 2002-88177	20020314
HK 1045696	A1	20031121	HK 2002-107336	20021007
US 2004171870	A1	20040902	US 2003-725820	20031201
PRIORITY APPLN. INFO.:			SE 1999-3345	19990917
			WO 2000-GB3473	20000911
			US 2002-88177	20020314

OTHER SOURCE(S): MARPAT 134:252473

AB The process claimed for the preparation of salts of substituted or unsubstituted methylenebisphosphonic acids (X1X2C(P(O)(OH)2)2; X1 and X2 are independently H, halogen) comprises hydrolyzing the corresponding acid ester (X1X2C(P(O)(OR)2)2; R = C1-4 straight or branched chain alkyl) with HCl and removing H2O from the acid azeotropically prior to addition of an amine or a base. An example preparation follows. Tetraisopropyl dichloromethylenebis(phosphonate) (0.024 mol) was dissolved in 18% HCl (30 mL). The resultant solution was added dropwise to a stirred heated (85°) solution of 18% HCl (10 mL). The solution was then stirred at 85° for 2 h under a flow of N2 while collecting the distillate (iso-Pr chloride). After this time the temperature was raised and the acid distilled off until the min. volume was reached (15 mL for this experiment). Put
and take with H2O was done keeping the volume as low as possible (13 x 3 mL portion). The reaction mixture was then cooled prior to the addition of BuOH

(20 mL). Vacuum was applied to the vessel and the temperature raised to remove the H2O/BuOH, keeping the temperature <100°. Solvent was again removed until the min. volume was reached. This was repeated by the addition of two further portions of BuOH (20 mL). The solution was then diluted with BuOH to give the product in a total volume of 41 mL. To this solution was added EtOH (9 mL) to give the product at a concentration of 6 mL/g in 15% EtOH/BuOH. The reaction mixture was then treated with tri-n-butylamine (1.0 equiv). The reaction mixture was stirred overnight. The suspension was then filtered and the solid washed with BuOH (3 mL). The damp solid was dried in vacuo at 80°C overnight to give dichloromethylenebis(phosphonic acid) mono(tri-n-butylamine) salt as a white solid in excellent yield (9.27 g, 89%).

RX(1) OF 12



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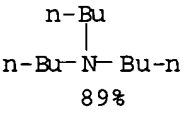
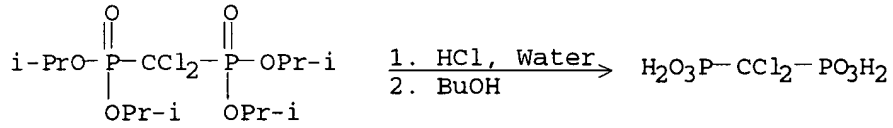


RX(3) OF 12



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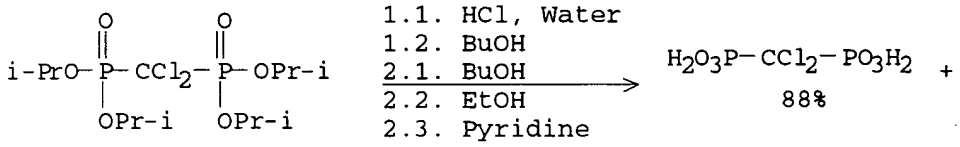
RX(8) OF 12 - 2 STEPS



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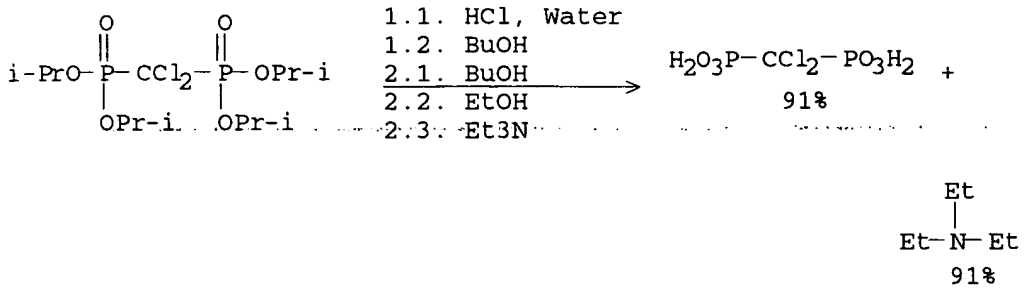
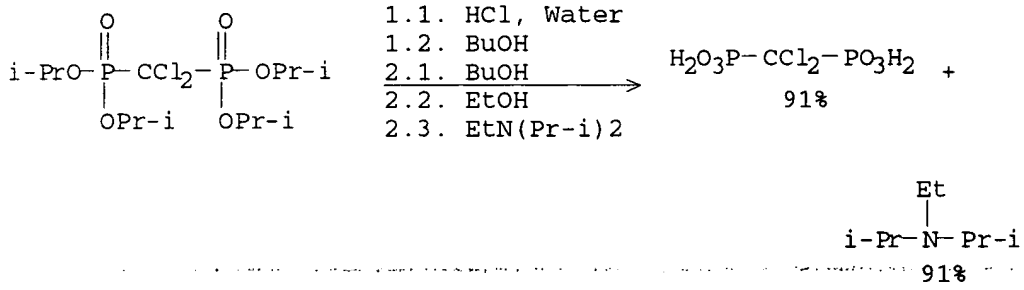
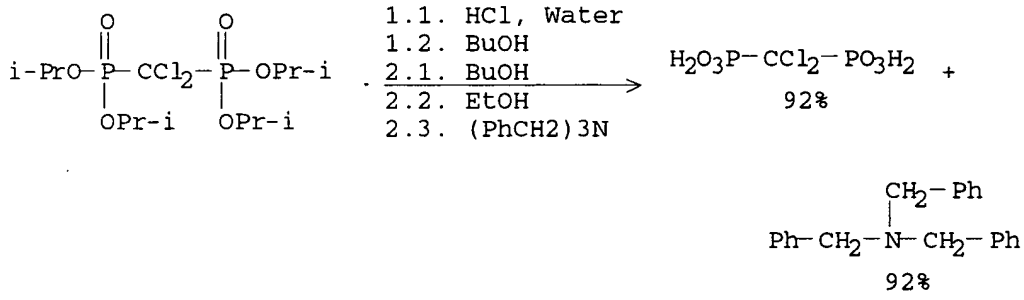
RX(9) OF 12 - 2 STEPS



RX(10) OF 12 - 2 STEPS



RX(11) OF 12 - 2 STEPS



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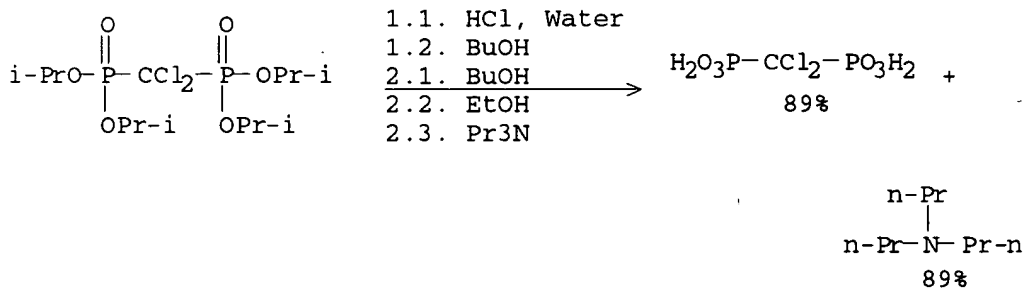
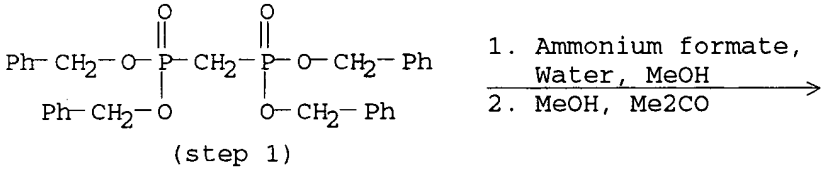


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 123:112201 CASREACT
TITLE: First use of benzyl phosphites in the Michaelis-Arbuzov reaction synthesis of mono-, di-, and triphosphate analogs
AUTHOR(S): Saady, Mourad; Lebeau, Luc; Mioskowski, Charles
CORPORATE SOURCE: Faculte de Pharmacie, Universite Louis Pasteur de Strasbourg, Illkirch, F-67401, Fr.
SOURCE: Helvetica Chimica Acta (1995), 78(3), 670-8
CODEN: HCACAV; ISSN: 0018-019X
PUBLISHER: Verlag Helvetica Chimica Acta
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Benzyl phosphites were used in the Michaelis-Arbuzov reaction with, e.g., ROP(O)(CH2Cl)2 (R = PhCH2) to give ROP(O)[CH2P(O)(OBn)2]2. Special exptl. conditions gave a set of phosphonate analogs of mono-, di-, and triphosphate. Also, regioselective mono-deprotection makes these mols. useful building blocks for the synthesis of analogs of polyphosphorylated compds. of biol. interest (e.g. nucleotides), after removal of all phosphonate benzyl ester groups under very mild conditions and high yields.

RX(17) OF 82



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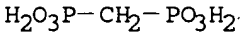


94%

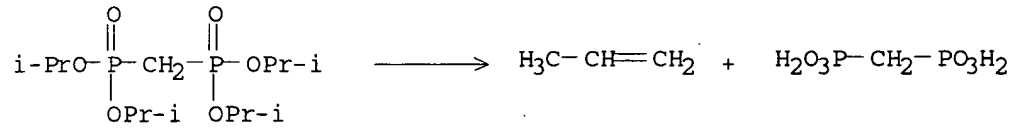
L3 ANSWER 5 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 121:109264 CASREACT
TITLE: Process for preparing methylenediphosphonic acid
INVENTOR(S): Budsky, Frantisek; Prokop, Jiri; Zobacova, Alena
PATENT ASSIGNEE(S): Ustav Jaderneho Vyzkumu, Czech.
SOURCE: Czech., 3 pp.
CODEN: CZXXA9
DOCUMENT TYPE: Patent
LANGUAGE: Czech
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CS 276850	B6	19920812	CS 1990-3593	19900719

PRIORITY APPLN. INFO.: CS 1990-3593 19900719
AB The title compound CH2(PO3H2)2 (I), useful as a chelating agent, is more

conveniently and directly prepared from CH2Br2 (II) and P(OPr-iso)3 (III) by thermal elimination reaction of the intermediate tetraester CH2[P(O)(OPr-iso)2]2 (IV) at 188-195°. The reaction produces propene gas and a residue, from which I is removed by dissoln. in AcOH and crystallization The method gives I in high yield and purity, and is faster and easier than the usual saponification of IV, which involves heating the ester for at least 8 h with concentrated HCl. For example, II and III were gradually heated together to 150-160° over approx. 6 h, and the reaction was maintained at that temperature until all formed iso-PrBr had distilled (usually 4-6 h). The mixture was then carefully heated to 188-195°, observing a decline in temperature (approx. 30°) and vigorous evolution of propene, after which the mixture was reheated and maintained at the same temperature until all propene had escaped. The cooled residue was extracted with the min. amount of boiling AcOH, and the solution concentrated and cooled to give crystalline I.

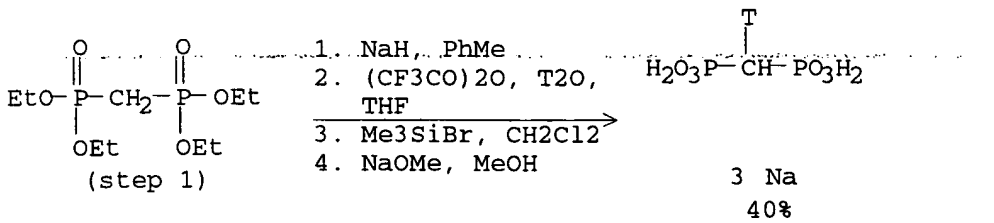
RX(2) OF 2



NOTE: 188-195.degree. with vigorous evolution of propene

L3 ANSWER 6 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 119:250029 CASREACT
TITLE: Synthesis of deuterium- and tritium-labeled methylenediphosphonic acid
AUTHOR(S): Yakovleva, G. M.; Rosenberg, S. G.; Blackburn, G. M.
CORPORATE SOURCE: Branch Shemyakin Inst. Bioorg. Chem., Pushchino, Russia
SOURCE: Bioorganicheskaya Khimiya (1992), 18(12), 1544-50
CODEN: BIKHD7; ISSN: 0132-3423
DOCUMENT TYPE: Journal
LANGUAGE: Russian
AB A facile method for preparing methylene-group tritiated methylenediphosphonic acid (30 Ci/mol, 40% radiochem. yield) was based on model studies of the deuteration of [(EtO)2P(O)CHP(O)(OEt)2]-Na+ with D2O/(CF3CO)2O.

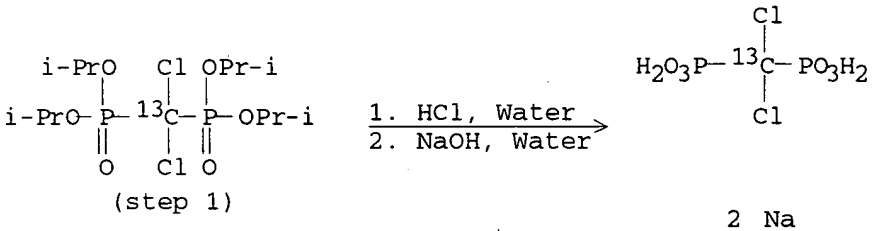
RX(2) OF 2



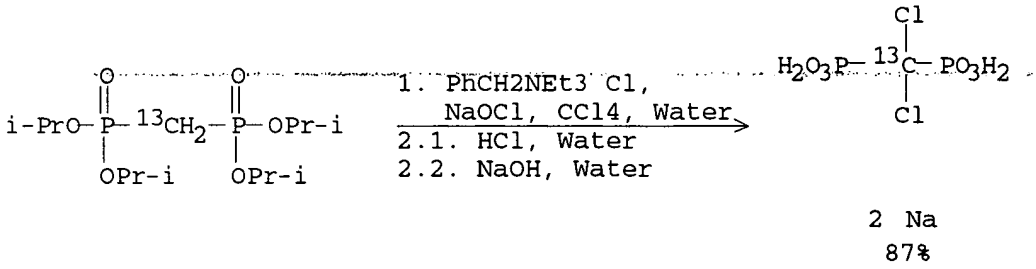
L3 ANSWER 7 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 116:41591 CASREACT
TITLE: Bisphosphonic compounds. I. Preparation of 13C- and 14C-labeled clodronate
AUTHOR(S): Jouko, Vepsalainen; Heikki, Nupponen; Esko, Pohjala
CORPORATE SOURCE: Dep. Chem., Univ. Kuopio, Kuopio, SF-70211, Finland
SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals (1991), 29(11), 1191-6
CODEN: JLCRD4; ISSN: 0362-4803
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tetrakis(1-methylethyl) (methylene-13C)bisphosphonate was obtained from 13C-Me iodide via the Michaelis-Arbuzov reaction with tris(1-methylethyl) phosphite followed by condensation with chlorophosphonic acid bis(1-methylethyl)ester. Tetrakis(1-methylethyl) (methylene-14C)bisphosphonate was prepared from 14C-dibromomethane via the Michaelis-Arbuzov reaction with excess of tris(1-methylethyl) phosphite. Both of these labeled tetraesters were chlorinated with NaOCl, hydrolyzed with HCl and neutralized with NaOH similarly. The overall yield of 13C-clodronate, (dichloromethylene-13C)bisphosphonic acid disodium salt tetrahydrate, was 71% with 99.5% isotopic and 99.8% chemical purity. The overall radiochem. yield of 14C-clodronate was 9.8%.

RX(3) OF 11



RX(7) OF 11 - 2 STEPS

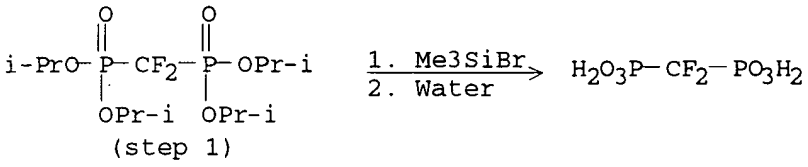


L3 ANSWER 8 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 110:114937 CASREACT
TITLE: A simple synthesis of monofluoromethylenebis(phosphonic acid)
AUTHOR(S): Hutchinson, David W.; Thornton, David M.
CORPORATE SOURCE: Dep. Chem., Univ. Warwick, Coventry, CV4 7AL, UK
SOURCE: Journal of Organometallic Chemistry (1988), 340(1), 93-9

CODEN: JORCAI; ISSN: 0022-328X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A simple synthesis of monofluoromethylenebis(phosphonic acid) has been devised, starting with an Arbuzov reaction between fluorotribromomethane and triisopropyl phosphite to give diisopropyl dibromofluoromethylphosphonate. A Michaelis-Becker reaction between the latter and an excess of the sodium salt of diisopropyl phosphate yields tetraisopropyl bromofluoromethylene bisphosphonate, which is not isolated but undergoes nucleophilic debromination and protonation during the reaction and subsequent work up to produce tetraisopropyl monofluoromethylenebisphosphonate. De-esterification of the tetraester with bromotrimethylsilane followed by hydrolysis and cation exchange chromatog. gives di(triethylammonium)monofluoromethylenebisphosphonate, which is converted into the free acid by further ion exchange chromatog.

RX(7) OF 20



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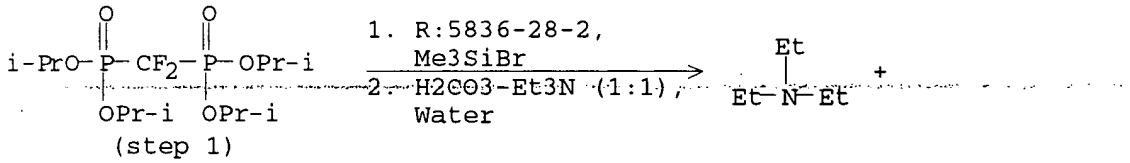
RX(8) OF 20



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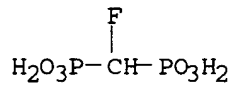

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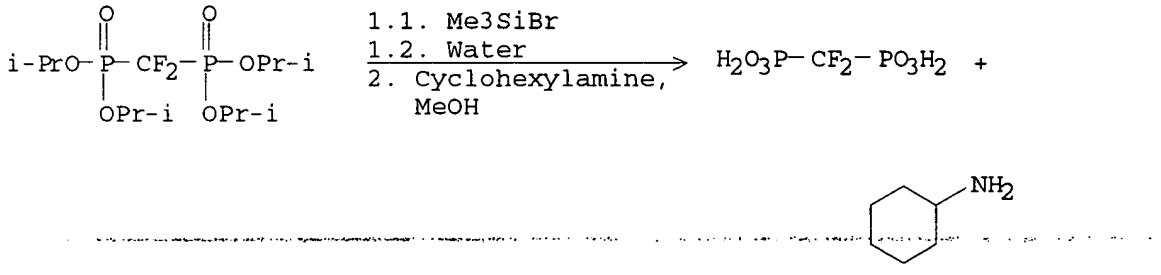

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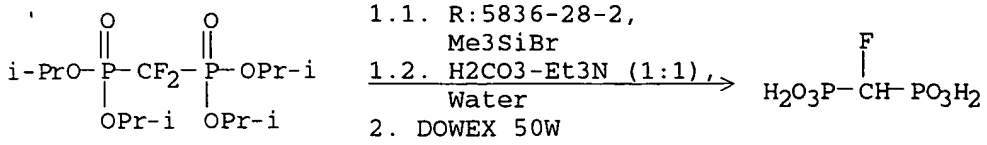
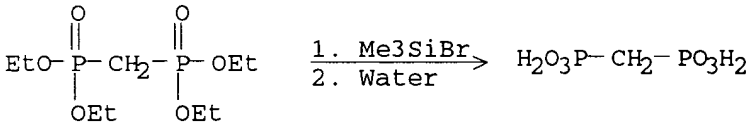


L3 ANSWER 9 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 107:39938 CASREACT
TITLE: Synthesis of phenoxy derivatives of methanediphosphonic acid
AUTHOR(S): Lang, G.; Herrmann, E.
CORPORATE SOURCE: Sekt. Chem., Tech. Univ. Dresden, Dresden, DDR-8027, Ger. Dem. Rep.
SOURCE: Zeitschrift fuer Anorganische und Allgemeine Chemie (1986), 536, 187-96
CODEN: ZAACAB; ISSN: 0044-2313
DOCUMENT TYPE: Journal
LANGUAGE: German
AB Michaelis-Arbuzov reaction of ICH2P(O)(OPh)n(OEt)2-n (n = 0-2) with (EtO)P(OPh)m(OEt)2-m (m = 0-2) gave all 6 corresponding R2-m(PhO)mP(O)CH2P(O)(OPh)nR2-n (I; R = OEt). Silylating I (R = OEt) with Me3SiBr gave I (R = OSiMe3), which yielded I (R = OH) (II) on hydrolysis. II were reesterified to I (R = OEt) by heating with HC(OEt)3, and silylated back to I (R = OSiMe3) with HN(SiMe3)2. II were chlorinated by PCl5 to give I (R = Cl), which were hydrolyzed back to II. I (R = Cl) were also prepared by condensing NaOPh with CH2[P(O)Cl2]2.

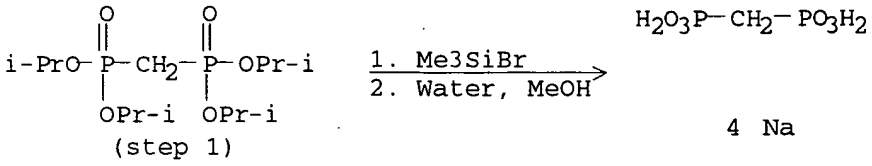
RX(54) OF 125 - 2 STEPS



L3 ANSWER 10 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 104:149010 CASREACT
TITLE: Synthesis of alkylated methylene bisphosphonates via organothallium intermediates
AUTHOR(S): Hutchinson, David W.; Semple, Graeme
CORPORATE SOURCE: Dep. Chem., Univ. Warwick, Coventry, CV4 7AL, UK
SOURCE: Journal of Organometallic Chemistry (1985), 291(2), 145-51
CODEN: JORCAI; ISSN: 0022-328X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Treating bisphosphonates (Me2CHO)2P(O)CHXP(O)(OCHMe2)2 (X = Cl, Br) with TlOEt, followed by alkyl iodides, gave good yield of (Me2CHO)2P(O)CRXP(O)(OCHMe2)2 (R = Me, Bu, etc.). The latter were hydrolyzed by use of BrSiMe3 and the tetrasodium salt were formed by iron

exchange chromatog.

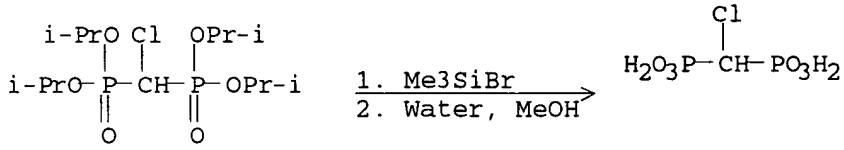
RX(17) OF 36



(step 1)

NOTE: final step involves ion exchange chromatog.

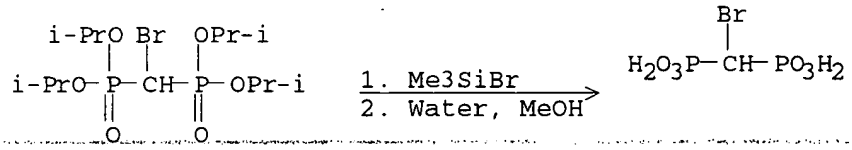
RX(18) OF 36



(step 1)

NOTE: final step involves ion exchange chromatog.

RX(20) OF 36



(step 1)

NOTE: final step involves ion exchange chromatog.

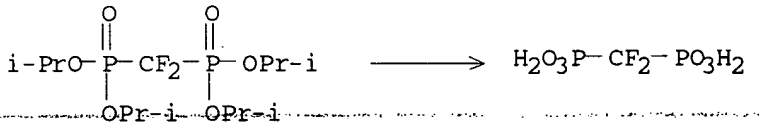
L3 ANSWER 11 OF 12 CASREACT COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 100:175062 CASREACT
TITLE: Pharmacologically active bisphosphonates and pharmaceuticals containing these substances
PATENT ASSIGNEE(S): Instituto Gentili S.p.A., Italy
SOURCE: Belg., 24 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: Dutch
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 896453	A2	19830801	BE 1983-60071	19830414
CH 661437	A	19870731	CH 1983-1654	19830325
GB 2118042	A1	19831026	GB 1983-8791	19830330
GB 2118042	B2	19860115		
FR 2525223	A1	19831021	FR 1983-5858	19830411

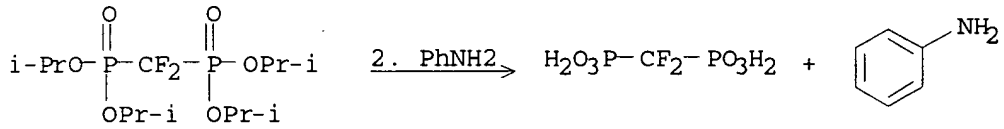
FR 2525223	B1	19860425		
DE 3313049	A1	19831117	DE 1983-3313049	19830412
DE 3313049	C2	19910725		
JP 58189193	A2	19831104	JP 1983-65160	19830413
JP 02013645	B4	19900404		
SE 8302130	A	19831016	SE 1983-2130	19830415
SE 463239	B	19901029		
SE 463239	C	19910221		
NL 8301324	A	19831101	NL 1983-1324	19830415
NL 192562	B	19970602		
NL 192562	C	19971003		
PRIORITY APPLN. INFO.:			IT 1982-20781	19820415
			IT 1983-1403	19830216

AB Phosphonylation of H2N(CH2)nCO2H (n = 3, 4) gave H2N(CH2)nC[P(O)(OH)2]2OH (I). Thus, H2N(CH2)4CO2H 9.4, P(OH)3 9.9, and POCl3 16.5 in PhCl gave I (n = 4) 12.4 kg. F2C[P(O)(OH2]2 was also prepared I inhibited urinary calculus. The LD50 for I (n = 3) was >2,000 mg/kg per os in mice.

RX(2) OF 7



RX(6) OF 7 - 2 STEPS

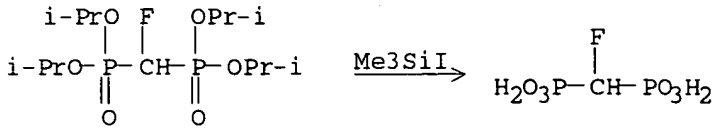


L3 ANSWER 12 OF 12 CASREACT COPYRIGHT 2005 ACS on STN

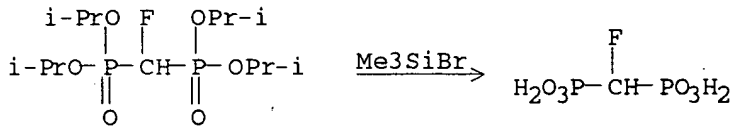
ACCESSION NUMBER:	96:35405 CASREACT
TITLE:	Monofluoro- and difluoromethylenebisphosphonic acids: isopolar analogs of pyrophosphoric acid
AUTHOR(S):	Blackburn, G. Michael; England, David A.; Kolkmann, Friedrich
CORPORATE SOURCE:	Dep. Chem., Univ. Sheffield, Sheffield, S3 7HF, UK
SOURCE:	Journal of the Chemical Society, Chemical Communications (1981), (17), 930-2 CODEN: JCCCAT; ISSN: 0022-4936
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB XCF[P(O)(OH)2]2 (X = H, F) were prepared by fluorinating CH2[P(O)(OH)2]2 with FClO3, and by condensing bromodifluoromethylphosphonate esters with NaP(O)(OBu)2 (I). E.g., fluorination of CH2[P(O)(OCHMe2)2]2 (NaH, PhMe, followed by FClO3, THF, -20°) gave a good yield of a 4:1 mixture of XCF[P(O)(OCHMe2)2]2 (X = H, F, resp.), whereas condensation reaction of BrCF2P(O)(OEt)2 with I (hexane, -40°) gave 45% of a mixture of (RO)2P(O)CF2PO(OR1)2 (R, R1 = Et, Bu). The 31P and 13C NMR spectra of the bisphosphonic acids prepared are reported.

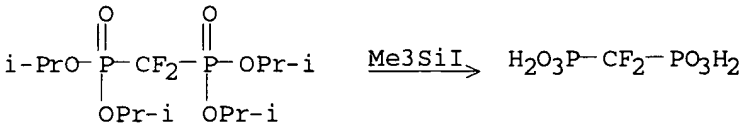
RX(3) OF 10



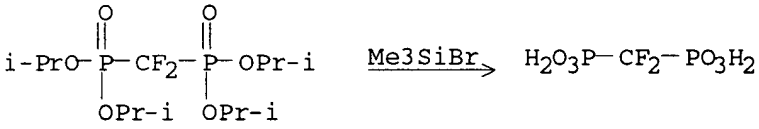
RX(4) OF 10



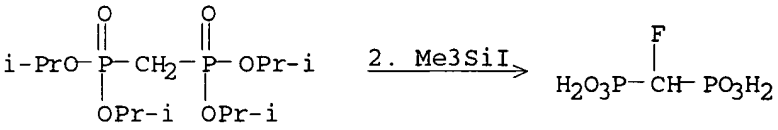
RX(5) OF 10



RX(6) OF 10



RX(9) OF 10 - 2 STEPS



RX(10) OF 10 - 2 STEPS